

### ***Remarks***

#### ***Status of the Claims***

Claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 are pending in the application, with claims 35, 39, 52, 69 and 72 being the independent claims.

#### ***Summary of the Office Action***

In the Office Action dated October 21, 2005, the Examiner has made four rejections of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

#### ***The Rejections under 35 U.S.C. § 102(b) Over Fukushima***

In the Office Action at pages 2-6, the Examiner has rejected claims 35-36, 35-49, 69, 72, 75, 79-82, 97, 99, 101-102, 107-108 and 110-111 under 35 U.S.C. § 102(b), over Fukushima, S. and Sauer, B., *Proc. Natl. Acad. Sci.* 89:7905-7909 (1992) (hereinafter "Fukushima"). Applicants respectfully traverse this rejection.

The Examiner asserts that Fukushima discloses a nucleic acid molecule comprising a *loxP* site separating a promoter (CMV) from an antibiotic resistance gene (NEO), wherein the *loxP* site is immediately adjacent to the NEO gene. The Examiner therefore concludes that Fukushima anticipates the presently claimed invention. Applicants respectfully disagree with these assertions and the Examiner's conclusions. The Examiner further states that "[t]hus, as to the rejected claims the only issue is whether Applicant's exclusive

interpretation of the limitation 'immediately adjacent' is correct." Office Action at page 4, third paragraph. Specifically, the Examiner states:

. . . there is no reason for interpreting the limitation "immediately adjacent" to mean that there is not a single nucleotide(s) between the claimed functional structures (e.g., CMV promoter and *loxP* site). Indeed, in observing the drawings, the claims and the disclosure on whole, and absent a definition to the contrary, the artisan would reasonably interpret the term "immediately adjacent" to mean two functional structures present next to each other without additional intervening functional structures.

Office Action at page 6, second paragraph. Applicants respectfully disagree with the Examiner's contentions.

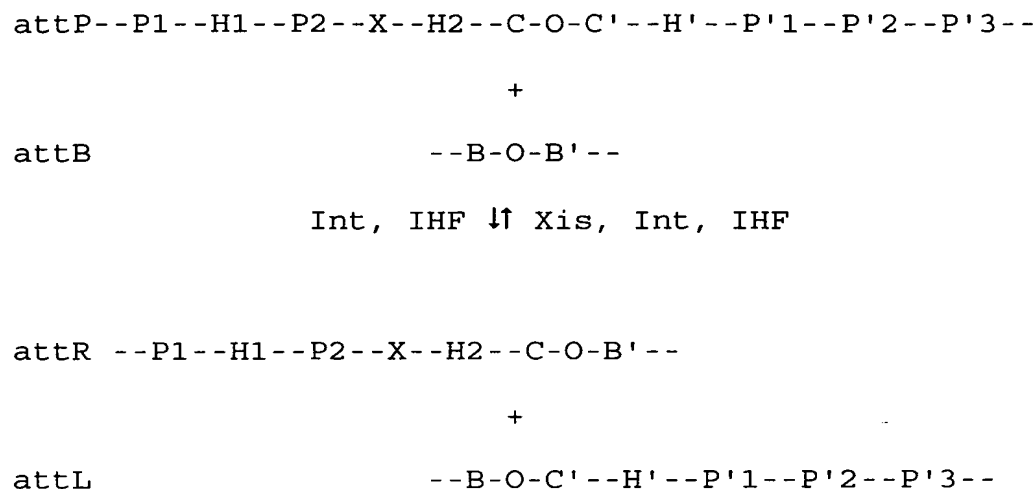
As noted in Applicants' reply filed on July 28, 2005, the disclosure of which is incorporated by reference herein in its entirety, the nucleic acid molecule represented in FIG. 2 of Fukushima, and referred to by the Examiner, clearly has intervening nucleotides between the CMV promoter and the *loxP* site. Hence, the CMV promoter is not *immediately adjacent* to the *loxP* site, as at least 25 nucleotides separate the CMV promoter from the *loxP* site. Hence, Fukushima does not disclose every element of the present claims, and therefore, cannot, and does not, anticipate the presently claimed invention. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

Applicants respectfully submit that the Examiner's interpretation of the term "immediately adjacent" is inconsistent with the interpretation that the ordinarily skilled artisan would give to that term in light of the present specification. The Examiner states

that the ordinarily skilled artisan would reasonably interpret the term "immediately adjacent" to mean that two functional structures are present next to each other without additional intervening functional structures between them. In making this statement, the Examiner refers to Figure 4C of the present specification, stating that the CMV promoter and the *loxP* site shown in this figure are "immediately adjacent." Applicants respectfully disagree with the Examiner.

As discussed in their previously reply, Applicants submit that Figure 4C clearly depicts an *SP6 promoter* located "immediately adjacent" to a *loxP* site. The CMV promoter referred to by the Examiner is *not* immediately adjacent to the *loxP* site, as there are clearly intervening nucleotides between the CMV promoter and the *loxP* site (e.g., the entire SP6 promoter). The Examiner's interpretation of a claim term must be consistent with the interpretation that those skilled in the art would reach in view of the teachings of the present specification. *See In re Cortright*, 165 F.3d 1353 (Fed. Cir. 1999); *see also* M.P.E.P. § 2111 at 2100-47. Applicants respectfully submit that, as noted above, based on the disclosure of the present specification, the ordinarily skilled artisan would readily understand that the SP6 promoter and the *loxP* site are immediately adjacent to one another, and as such, do not have any intervening nucleotides between them

Applicants would also like to note that, in the present Office Action, the Examiner has failed to address Applicants' discussion, in the previous reply, of the term "immediately adjacent" with reference to the schematic at page 38, lines 4-10 (reproduced below) representing the nucleotide regions that participate in an *att* recombination reaction in *E. coli*:



In describing this schematic, the present specification states that "O represents the 15 bp core DNA sequence found in both the phage and *E. coli* genomes; B and B' represent approximately 5 bases *adjacent* to the core in the *E. coli* genome;" (Specification at page 38, lines 11-13, emphasis added). Applicants respectfully submit that the ordinarily skilled artisan would readily understand, as stated, that B and B' are "adjacent" to the 15 bp core region "O," and as illustrated, that there are no intervening nucleotides between the core region, "O," and the 5 base pair B and B' regions (since no additional nucleic acids are shown in the schematic). The term "immediately" was added to the present claims to further clarify that two structures that are "adjacent" or "immediately adjacent" to one another are not simply "next to" one another, but rather are separated by no intervening nucleotides, as is clearly shown in the schematic above and in Figure 4C as discussed above.

Contrary to the Examiner's contentions, the ordinarily skilled artisan would not interpret the schematic and Figure 4 C, both in the present specification, to simply represent

that B and B' are next to the core in the *E. coli* genome without additional intervening functional structures, but with one or more intervening nucleotides. Indeed the only way that the recombinational cloning reaction depicted in this schematic could result in the recombination products depicted would be if regions B and B' were *not* separated from the core (O region) by any intervening nucleotides, i.e., if they were "immediately adjacent" to the core region. Any intervening nucleotides (let alone any functional structure) between the core "O" region and the B and B' regions would necessarily be involved in the recombination reaction, and therefore, would be present in the resulting products. Since such intervening nucleotides are not shown in the products, they cannot be present between the "O" and "B and B'" regions in the starting molecules. Applicants respectfully submit that the only interpretation that the ordinarily skilled artisan could possibly give to the schematic at page 38 showing B and B' "approximately 5 bases *adjacent* to the core in the *E. coli* genome" is that there are no intervening nucleotides between B and B' and the core O region. The Examiner has provided no actual evidence that a contrary interpretation is proper, relying instead on pure speculation.

Applicants respectfully submit, as noted above, Fukushige clearly does not disclose a nucleic acid molecule in which a *lox* site is located immediately adjacent to at least one promoter, or a promoter immediately adjacent to a site-specific recombination site. Hence, Fukushige does not disclose every element of the present claims, and under *Kalman*, cannot and does not anticipate the presently claimed invention. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C § 102(b) are respectfully requested.

***The Rejections under 35 U.S.C. § 102(e) Over Wahl***

In the Office Action at pages 6-8, the Examiner has rejected claims 39, 43, 47-49, 79, 81, and 101-102 under 35 U.S.C. § 102(e), over Wahl et al., U.S. Patent No. 5,677,177 (hereinafter "Wahl"). Applicants respectfully traverse this rejection.

The Examiner asserts that Wahl discloses a nucleic acid molecule comprising a promoter element (P or PSV) separated from an antibiotic resistance gene (NEO) by a site-specific recombination site (FLP target sites), where the FLP target site is immediately adjacent to the promoter or the antibiotic resistance gene. The Examiner contends that since Wahl allegedly discloses a nucleic acid molecule where a promoter and an antibiotic resistance gene are next to a site-specific recombination site, and since the term "immediately adjacent" allegedly is not interpreted to mean that there can be no intervening nucleotides between two functional elements on a nucleic acid molecule, Wahl therefore anticipates the presently claimed invention. Applicants respectfully disagree with the Examiner's conclusions and the contentions on which they are based.

Applicants respectfully submit that Wahl does not disclose a nucleic acid molecule comprising a promoter operably linked to an antibiotic resistance gene, and separated by a site-specific recombination site, wherein the promoter is also immediately adjacent to the site-specific recombination site. Wahl, specifically FIGs. 1A-1B, 2A and 3A, does not disclose a nucleic acid molecule where a promoter (P or PSV) is immediately adjacent to the site-specific recombination site (FRT sites indicated by block arrows) that separates the promoter from the antibiotic resistance gene.

As discussed above, and in Applicants' reply filed July 28, 2005, the term "immediately adjacent," as it is used in the present claims and specification, means that there

are no intervening nucleotides between two structures, in this case, between the promoter and the site-specific recombination site separating the promoter from the antibiotic resistance gene. The nucleic acids disclosed in Wahl clearly show the presence of intervening nucleotides between the promoter and the FRT site (block arrow). The PSV promoter indicated in FIGs. 1A and 2A is not immediately adjacent to the FRT site, as the FRT site is inserted *within* the  $\beta$ -gal coding sequence (*i.e.*, downstream of the translation start site). Hence, there are intervening nucleotides between the PSV promoter and the FRT site-specific recombination site, and thus these two structures are not "immediately adjacent" to one another, as recited in the present claims. Therefore, Wahl does not disclose every element of the present claims, and under *Kalman*, cannot and does not anticipate the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the rejection of claims 39, 43, 47-49, 79, 81, and 101-102 under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

***The Rejection Under 35 U.S.C. § 103(a) Over Fukushima and Wahl and Further in View of Lenski***

In the Office Action at pages 9-11, the Examiner has rejected claims 35-36, 38-51, 65-66, 69-75, 79-86, 92-93, 95-103 and 107-112 under 35 U.S.C. § 103(a), over Fukushima and Wahl and further in view of Lenski, R.E., *et al.*, *J. Bact.* 176:3140-3147 (1994). Applicants respectfully traverse this rejection.

The Examiner states that Fukushima and Wahl do not explicitly disclose the use of chloramphenicol as an antibiotic resistance gene, or the use of bacterial host cells, such as

*E. coli*. The Examiner relies on the disclosure of Lenski to allegedly cure these deficiencies, asserting that it would have been obvious to use different antibiotic resistance genes in the practice of Fukushige and Wahl, and that it would have been obvious to use a bacterial cell, such as *E. coli*, in combination with these references as well. The Examiner therefore concludes that the present invention is rendered obvious in view of these references. Applicants respectfully disagree with this conclusion.

As noted above, Fukushige and Wahl are seriously deficient as primary references on which to base a *prima facie* case of obviousness, as neither reference discloses the recited nucleic acid molecules and host cells. Specifically, neither reference discloses a nucleic acid molecule comprising a promoter *immediately adjacent* to a site-specific recombination site that separates the promoter from an antibiotic resistance genes. Applicants respectfully submit that, while it may disclose the use of a chloramphenicol antibiotic resistance gene in combination with *E. coli* cells, Lenski does not disclose nucleic acid molecules comprising a promoter *immediately adjacent* to a site-specific recombination site. Hence, Lenski does not cure the deficiencies in Fukushige and Wahl, and therefore cannot provide support for a *prima facie* case of obviousness.

As the Examiner has noted, whether the primary references are deficient once again turns on the interpretation of the term "immediately adjacent." For at least the reasons detailed above, Applicants respectfully submit that the ordinarily skilled artisan would readily understand the term "immediately adjacent" to mean that there are no intervening nucleotides between the recited functional elements. There can be no other meaning given to this term based upon the disclosure of the present specification. As noted above, the only interpretation of the schematic at page 38 showing functional elements "adjacent" to one

another is that there are no intervening nucleotides between the O core regions and the B and B' regions. Similarly, the ordinarily skilled artisan would readily understand that the SP6 promoter and the *loxP* site depicted in Figure 4C of the present specification are immediately adjacent to one another with no intervening nucleotides between them. Any other interpretation of the term "immediately adjacent" as it is used in the present claims, would be inconsistent with the use of this term throughout the present specification.

In view of the foregoing remarks, Applicants respectfully submit that Fukushima, Wahl and Lenski, alone or in combination, do not render obvious the presently claimed invention. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

***The Rejection Under 35 U.S.C. § 103(a) Over Fukushima, Wahl and Lenski and Further In View of Griffiths***

In the Office Action at pages 11-13, the Examiner has rejected claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 under 35 U.S.C. § 103(a), over Fukushima, Wahl and Lenski, and further in view of Griffiths *et al.*, U.S. Patent No. 5,962,255 (hereinafter "Griffiths"). Applicants respectfully traverse this rejection.

The Examiner states that Fukushima, Wahl and Lenski do not explicitly disclose that the site-specific recombination sites can be lambdoid *att* sites. The Examiner relies on the disclosure of Griffiths to allegedly cure this deficiency. The Examiner contends that, as far as site-specific recombination systems are concerned, lambda phase *att* sites are routinely utilized in the relevant art interchangeably with other site-specific recombination systems (e.g., Cre/*lox*, FLP/*FRT*). The Examiner further contends that Griffiths discusses both the

*lox* and *att* systems in the context of site-specific recombination as interchangeable equivalents. The Examiner therefore concludes that it would have been obvious to modify the expression vectors disclosed in Fukushima or Wahl to obtain the benefit of extending the range of site-specific recombination systems, and that hence, the presently claimed invention is rendered obvious. Applicants respectfully disagree with the Examiner's conclusions and the contentions on which they are based.

While the disclosure of Griffiths does indicate that both the *Cre/lox* system and the *Int/att* system are recombinational cloning systems, Griffiths makes no indication that one should, or even could, consider substituting the *Int/att* system for the *FLP/FRT* system utilized in Wahl, or the *Cre/lox* system disclosed in Fukushima. In fact, there is no mention of the *FLP/FRT* system at all in Griffiths, much less the motivation required to substitute the *Int/att* site for the *FLP/FRT* system.

Instead, Griffiths states that "[f]or the work described in this application, the *loxP/Cre* system was chosen of the alternatives available because the recombination is highly sequence-specific, very efficient and occurs at a short target site that is readily incorporated into cloning vectors." Griffiths at column 19, lines 55-59. Hence, Applicants respectfully submit that Griffiths does not provide any mention or motivation to substitute the *Int/att* system for the *FLP/FRT* system utilized in Wahl, or the *Cre/lox* system utilized in Fukushima. In fact, Griffiths clearly teaches away from such substitutions, as Griffiths favors the use of a *loxP/Cre* system above "the alternative available" (i.e., the *Int/att* system and the *FLP/FRT* system).

It is axiomatic that, in order to support a *prima facie* case of obviousness, the prior art must suggest making the specific molecular modifications necessary to achieve the

claimed invention. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lahu*, 747 F.2d 703, 705 (Fed. Cir. 1984) (“[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.”). That is, simply because “one can conceive a general process in advance for preparing an undefined compound [e.g., a genetic construct comprising “a regulatory sequence”] does not mean that a claimed specific compound [e.g., a genetic construct comprising “a regulatory sequence which responds to a change in intracellular concentration of one or more second messengers”] was precisely envisioned and therefore obvious.” *Deuel* at 1559. Thus, in order for either Wahl, Fukushige or Griffiths to be suitable as primary references upon which to base a *prima facie* case of obviousness, there must be, at a minimum, a teaching or suggestion in these references that would compel one of ordinary skill in the art to substitute the *Int/att* system for the *FLP/FRT* system or the *Cre/lox* system. As noted above, such a teaching or suggestion is wholly lacking in Wahl, Fukushige and Griffiths. Therefore, these documents are seriously deficient as a primary references (particularly in view of the holding in *Deuel*), and cannot support a *prima facie* case of obviousness.

Hence, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness based on the disclosures of Fukushige, Wahl, Lenski and Griffiths, alone or in combination. Reconsideration and withdrawal of the rejection of claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 under 35 U.S.C. § 103(a) are therefore respectfully requested.

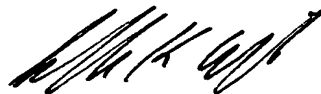
***Conclusion***

All of the stated grounds of rejection have been properly traversed or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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